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Multi-scale modeling reveals use of hierarchical tensegrity principles at the molecular, multi-molecular, and cellular levels

Charles B. Reilly [a], Donald E. Ingber [a,b,c,*]

[a] Wyss Institute for Biologically Inspired Engineering at Harvard University, Boston, MA 02115, USA
[b] Vascular Biology Program and Department of Surgery, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, USA
[c] Harvard John A. Paulson School of Engineering and Applied Sciences, Cambridge, MA 02139, USA

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ABSTRACT

Mechanobiology – the discipline that focuses on the key role that mechanical forces contribute to control of biological structure and function across all size scales – requires application of multi-disciplinary approaches. These approaches span multiple fields including materials science, physics, chemistry, biology, engineering, medicine and computational modeling. Mechanobiology has been significantly advanced by the cellular tensegrity theory. This theory proposes that living systems use principles of tensegrity architecture to govern how molecules self-assemble to create multi-molecular structures, organelles, cells, tissues, organs and living organisms. Use of tensegrity provides a mechanism to control shape stability while maintaining tight integration between structure and function. It also enables mechanical information transfer from the macro-scale to the nanoscale, where mechano-chemical transduction can occur at the molecular level. While various experiments have provided data in support of the use of tensegrity by biological systems, it has not been possible to visualize how these architectural principles are utilized to build hierarchical structures of various sizes and complexity that undergo dynamic changes in form and mechanics within living cells. We recently described a new advance in multi-scale molecular simulation that combined molecular dynamic simulation methods with physics-based animation approaches, which showed how mechanical forces and deformations generated at the molecular level propagate across size scales to drive directional movement of whole cells, using sperm motility as an example (Reilly and Ingber, *ACS Nano* 2017, 11:12156–12166). These computer simulations also confirmed that tensegrity principles are indeed utilized at the level of individual molecules, multi-molecular assemblages, and whole living cells. Here, we explore these previous findings in greater detail in relation to tensegrity, and also describe how this simulation strategy can be used to model coupling of enzyme substrate concentrations to multiscale tensegrity-based force transduction, using mitochondrial ATP synthase as an example.

Contents

1. Introduction

The field of Mechanobiology is of extreme importance because mechanical forces play a significant a role as chemicals and genes

* Correspondence to: Wyss Institute for Biologically Inspired Engineering at Harvard University, CLSB5, 3 Blackfan Circle, Boston, MA 02115, USA.
E-mail address: don.ingber@wyss.harvard.edu (D.E. Ingber).

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when it comes to controlling the structure and function of living systems. Some of the central questions in the field relate to how physical forces govern the shape, mechanics and function of individual molecules, multi-molecular cytoskeletal structures, organelles, cells, tissues, organs and whole organisms. However, as all of these structures form and function as hierarchically integrated mechano-chemical systems, we must understand how living systems establish their shape stability and integrate structural and functional changes across multiple size scales in order to answer these questions. But this challenge is beyond most conventional scientific paradigms and experimental methodologies which commonly rely on reductionistic approaches (*i.e.*, understanding the parts will lead to meaningful insight into the whole), and thus little is known about multi-scale mechanical integration within living cells and organisms.

Over thirty five years ago, we first suggested that living systems may use the principles of tensegrity (tensional integrity) architecture to guide their self assembly and hierarchical integration, as well as control their shape stability and carry out mechano-chemical transduction [1–12]. Tensegrity is a building principle that was first described by the architect R. Buckminster Fuller [13] and first visualized by the sculptor Kenneth Snelson [14], which describes multi-component structures that establish their shape stability (e.g., mechanical stiffness and three-dimensional form) through establishment of a "prestress" (preexisting tensile stress or isometric tension), rather than by continuous compression (e.g., as used in a stone arch). Because most tensegrities have been constructed as prestressed "bar and cable" structures where the bars to do not touch (Fig. 1(A)), many have described a tensegrity structure as a tensed network of structural members that resists shape distortion and self-stabilizes by incorporating other support elements that resist compression (e.g., structures that establish their shape through continuous tension and local compression). However, rigid struts are not required as similar tensegrity structures can be constructed entirely from different types of flexible springs that simply differ in their elasticity (Fig. 1(B)). In these structures, the semi-flexible springs shorten or buckle when compressed, while others lengthen when under tension.

Tensegrities are notably responsive to outside perturbation as when force is applied locally, all the components that comprise the structure reorient resulting in an integrated structural response and change in form. Moreover, this response fully reverses when the force is removed. Importantly, multiple small tensegrity structures can be combined using similar rules of tensional integrity to form larger tensegrity systems that exhibit similar mechanical and structural responses. And these larger tensegrities can self assemble to create even larger and more complex structures that again exhibit similar behaviors. When a force is applied to a single component in this type of hierarchical tensegrity structure, a redistribution of forces and rearrangement of elements that result can span across long distances and size scales throughout the tensionally-integrated system.

We and others have previously shown that living mammalian cells gain their shape stability through establishment of a state of isometric tension (prestress) in which tension forces generated actively by contractile microfilaments within the cytoskeleton are balanced by microtubules (MTs) and extracellular matrix tethers (to larger tissue level tensegrities) that resist inward-directed compressive forces [5,15–17]. The nucleus also has been shown to be a tensegrity structure, and when it is tensionally integrated within a living mammalian cell by molecular cytoskeletal filaments (*i.e.*, intermediate filaments, actin filaments and microtubules) that physically couple the nuclear lamina to cell–cell and cell–matrix adhesion receptors on the cell surface, it becomes part of a larger hierarchical tensegrity structure at the cell level [18,19]. Moreover, experiments with living cells confirm that when force is applied locally to cell surface adhesion receptors, molecular components rearrange within the internal cytoskeleton and nucleus in a reversible manner, and these force-induced changes in molecular shape and position mediate mechano-chemical transduction [5,9,10,18,20–24]. In addition, tensegrity has been suggested to be used at the level of the whole organism, organs, and tissues as well as multi-molecular complexes (e.g., contractile microfilaments, cellular membranes) and even individual molecules based on physical models or computational approaches [7–10,25,26]. However, it has been difficult to visualize how tensegrity principles are utilized within hierarchical molecular structures that comprise living cells and organisms that undergo dynamic changes in shape and form. Here we describe how development of a new approach to multi-scale computational modeling confirms that tensegrity principles are used at multiple different size scales and across various levels of structural complexity within living cells. These simulations reveal how tensegrity-based changes in molecular shape can drive transformations in 3D cell shape and dynamic cellular motion at larger scales, using the mammalian sperm cell as a model system.

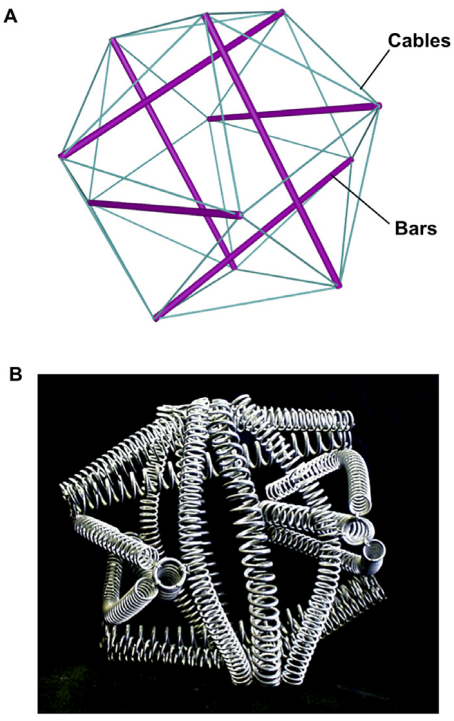

Fig. 1. Tensegrity models. (A) A 6-strut bar and cable model. (B) A force balanced tensegrity structure made entirely of cables of varying elasticity.

2. A new approach to multi-scale modeling

We developed a procedural computational modeling approach to achieve multiscale tensegrity depictions that span the extremely large and dynamic spatial and temporal ranges that are present in cellular and molecular systems. The fundamental concept behind this procedural approach is that the model itself is just a series of mathematical operations (operators). The parameters that feed into these operators can change, and these changes will propagate throughout the model. This approach allowed us to integrate many different kinds of data, including multiscale simulations of different systems that can be intertwined, where the output of a simulation at one size scale provides input variables for the next simulation at a different scale and level of complexity. Furthermore, these simulations can integrate experimental data of varying